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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,933	03/30/2001	Irving Goldschneider	883933.0023 (UCON-122)	7584

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CUMMINGS AND LOCKWOOD
GRANITE SQUARE
700 STATE STREET
P O BOX 1960
NEW HAVEN, CT 06509-1960

EXAMINER
MERTZ, PREMA MARIA

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/823,933	Goldschneider et al.
Examiner	**Art Unit**
Prema Mertz	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 9, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above, claim(s) *28-31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I (claims 1-27) in Paper No. 9 (8/9/02) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP. § 818.03(a)).

Claims 28-31 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim rejections-35 USC § 112, first paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 1-27 are genus claims. Claim 1, sub-part(a), recites a polypeptide which has greater than about 40% sequence identity with IL-7, and sub-part(b) recites a polypeptide which has greater

than about 40% sequence identity with the beta chain of HGF, which encompasses "variants" of these molecules. Claim 22 recites these same limitations. Claim 5 recites "a biologically-active variant" and claim 27 recites "a biologically active variant". The term variant means a nucleic acid molecule encoding a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to the DNA molecule which encodes the amino acid sequence (see page 8, lines 1-11). The specification and claims do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the nucleic acid molecule. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the cytokine IL-7 and the β chain of HGF alone are insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicants was not in possession of the claimed genus of IL-7 and β chain of HGF molecules.

2b. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a hybrid cytokine comprising IL-7, the β chain of HGF and an oligosaccharide linker which is a low molecular weight form of heparan sulfate, does not reasonably provide enablement for a hybrid cytokine as recited in claims 1, 5, 17, 18, 22, and 26-27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 5, 22 and 27, recite variants of the IL-7 and the β chain of HGF, which claims are overly broad, since no guidance is provided as to which of the myriad of polypeptide species encompassed by the claims will retain the desirable characteristics of the IL-7 and β chain of HGF polypeptides. Variants of each of the polypeptides can be generated by conservative or nonconservative changes, allelic, splice species or polymorphic variants (see page 8, lines 1-11). However, Applicants have failed to disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of IL-7 and the β chain of HGF. Moreover, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect

the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a IL-7 and the β chain of HGF polypeptide other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of the claims, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would

require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

With respect to claims 12-15 which recite "a method for treating lymphocyte-related disorders", these claims encompass leukemias and lymphomas, pancytopenia, myelodysplastic syndrome, and hereditary or acquired immunodeficiency disorders and myelosuppression (see page 18, lines 24-30). While the specification discloses the biological properties which the hybrid cytokine may be considered to exhibit (see pages 28-31), it provides no guidance as to whether the hybrid cytokine has the ability to treat all lymphocyte-related disorders including those caused by HIV infection. One would not have a reasonable expectation of successfully using the hybrid cytokine in all the methods consistent with the scope of the claims.

The specification discloses the effect of the hybrid cytokine on stimulating the proliferation and differentiation of pre-pro-B cells (Example 10, pages 28-31). However, the claims recite "treating lymphocyte-related disorders" which encompasses any and all conditions resulting from lymphocyte dysfunction. The instant specification is non-enabling for such a method in the absence of support to accomplish a specific purpose by administration of the hybrid cytokine. The recitation of the term "lymphocyte-related disorders" in the claims, also embraces specific autoimmunity, such as rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, thyroid disorders, diabetes mellitus or multiple sclerosis. Since the principle biological effects of administration of the cytokine would be to stimulate proliferation and differentiation of pre-pro-B cells, the ability of the hybrid cytokine to treat all these disparate disorders involving lymphocytes would not be an enabled

paradigm. The hybrid cytokine could not be administered with a predictable prognosis using the specification as guidance because the specification provides no examples nor is an enabling mechanism disclosed using the hybrid cytokine commensurate with the scope of the claims. In the absence of such a disclosure a skilled artisan would be unable to practice the methods embraced by the claims without undue experimentation.

The current specification as filed discloses that the hybrid cytokine may be used in *in vivo* treatment of acquired immunodeficiency disorders (see page 18, lines 24-29). The virus in question, HIV has been the subject of intense study for over a decade. Many promising treatments and therapies have been identified via *in vitro* experiments, and have not lived up to expectations when tested *in vivo*. In fact, the number of such treatments which have failed to live up to their promise exceeds those which have been performed as hoped by orders of magnitude. In view of this unpredictability in the treatment, therapy and prophylaxis of HIV infection, there cannot be said to be any reasonable expectation of success at the in vivo application of a potential therapy with the hybrid cytokine. Therefore, it would require undue experimentation for the ordinary artisan to determine how to use the hybrid cytokine *in vivo* in the treatment of HIV infection., a disease with an aberrant immune response. Treatment of HIV with the hybrid cytokine *in vivo* would have not been believable by one of ordinary skill in the art at the time of filing of the instant application. Applicant is advised to note Ex parte Balzarini 21 USPQ2d, 1892 at page 1897 (Bd. PAT. App. and Int. 1991):

We do not presume to tell appellants what evidence would be acceptable in rebuttal of these rejections. While we are not requiring human clinical trials, it may well be that in 1987 or even now those skilled in this art would not accept anything short of such human clinical trials. There is no evidence of record that experimental animal models have been developed in this area which would have been predictive of human efficacy.

During infection by HIV the virus replicates in the immune system, T lymphocytes expressing CD4 are preferred targets. In essence, there is selective loss of precisely those T cells that respond to and protect against environmental pathogens. In addition, there are multiple stages of HIV infection and progression of the disease. In Stage IV, the final stage of the disease, the patient has a $CD4^+$ PBL count of less than 200 cells per mm^3. In the absence of any teaching or guidance it would require undue experimentation by one of ordinary skill in the art to develop a method to ascertain and select at which step in the disease the instant peptide will still be effective to restore the immune response. After taking into consideration all these factors, the applicant has not provided any data predictive of treatment of HIV infection with the hybrid cytokine. What is claimed in the specification is an invitation to experiment without teaching how to use the invention as claimed.

Claims 12-15 also embrace treatment of leukemias and lymphomas. In the specification only the proliferation and differentiation of pro-B cells from IL-7 KO mice has been demonstrated (pages 28-31). However, these limited results are not sufficient to enable the breadth of the claims. The disclosure fails to teach one of ordinary skill in the art a method of treatment of leukemias and lymphomas. The effectivity of the hybrid cytokine administered to treat a sarcoma may not necessarily be effective against leukemia. In the absence of specific examples for these B-cell

malignancies, the effectivity of the hybrid cytokine in the therapeutic treatment of these conditions, it is not deemed predictable. One of ordinary skill in the art could not practice the invention because of the quantity of experimentation required in treatment of these types of cancers, including the effective dose of the hybrid cytokine required and the pharmacokinetics to deliver the hybrid cytokine to be of therapeutic value. Given the breadth of the claims, the claims are not commensurate with the scope of the supporting disclosure.

With respect to claims 17-18 and 22, the specification is enabling for a hybrid cytokine complex comprising only an oligosaccharide linker which is a low molecular weight form of heparan sulfate as the flexible linking moiety adjoining IL-7 and the β chain of HGF. In Example 8, pages 26-27, applicants have only disclosed the use of HS-derived oligosaccharides in the formation of the active hybrid cytokine complex. Therefore, a person of ordinary skill in the art would be unable to determine which other linking moieties are embraced by the claims without undue experimentation to determine which linkers would result in the formation of hybrid cytokine complexes possessing the desirable biological activities.

Claims 2-4, 6-16, 19-21, 23-25 are rejected under 35 U.S.C. 112, first paragraph, insofar as they depends on claims 1, 5, 22 and 27 for their limitations.

Claim rejections-35 USC § 112, second paragraph

3. Claims 11 an 17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is unclear for several reasons.

Claim 17 recites "rIL7" which is unclear. It is suggested that the entire term be recited in the claim.

Claim 11(1) recites "prokoryotic" rather than "prokaryotic".

Claim rejections-35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by WO 95/13393.

WO 95/13393 teaches therapeutic hybrid cytokines comprising a cytokine and a growth factor linked by a linking sequence ranging from 5-40 amino acids (see abstract; pages 6, 11). Cytokines like IL-11 and IL-6 are growth factors because they augment hematopoietic cell proliferation (see page 3, lines 25-30) and ciliary neurotrophic factor (CNTF) promotes neuron augmentation and neuronal differentiation (page 3, lines 31-37). Therefore, the hybrid cytokine disclosed in the reference meets the limitations of the hybrid cytokine recited in claim 5.

Claim rejections-35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/13393.

The teachings of WO 95/13393 have been set forth above in paragraph 4. However, WO 95/13393 is silent about a biological preparation in which 95% or 60% or 30% of the weight of the proteinaceous matter in the preparation comprises the hybrid cytokine complex.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to purify the hybrid cytokine complex preparation of the WO 95/13393 publication. To obtain a biological preparation in which 95% or 60% or 30% of the weight of the proteinaceous matter in the preparation comprises the hybrid cytokine complex identified by the WO 95/13393 publication, to facilitate the characterization of the hybrid cytokine complex, by employing those methods of protein extraction and purification that were old and well known in the art at the time that the instant invention was made, would have been *prima facie* obvious to an artisan in light of the WO 95/13393 publication.

PM 10/24/02

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
October 23, 2002